A NOSOCOMIAL OUTBREAK OF FLUOROQUINOLONE-RESISTANT SALMONELLA INFECTION

Sonja J. Olsen, Ph.D., M.S., Emilio E. DeBess, D.V.M., M.P.V.M., Teresa E. McGivern, B.S.,
Nina Marano, D.V.M., M.P.H., Tom Eby, B.A., Steve Mauvais, B.A., Vijay K. Balan, M.S.,
Gerald Zirnstein, Ph.D., Paul R. Cieslak, M.D., and Frederick J. Angulo, D.V.M., Ph.D.

ABSTRACT

Background Infection with fluoroquinolone-resistant strains of salmonella is rare, as is nosocomial salmonella infection. We describe the first recognized outbreak of fluoroquinolone-resistant salmonella infection in the United States, which occurred in two nursing homes and one hospital in Oregon.

Methods We interviewed medical staff and reviewed patients' charts and death certificates. In Nursing Home A we conducted a case–control study. Patients were defined as residents of the nursing home from whom fluoroquinolone-resistant *Salmonella enterica* serotype Schwarzengrund was isolated between February 1996 and December 1998. Controls were residents with similar medical conditions whose cultures did not yield salmonella.

Results Eleven patients with fluoroquinolone-resistant salmonellosis were identified at two nursing homes. In nine patients a urine culture was positive, in one a stool culture, and in one a wound culture. The index patient had been hospitalized in the Philippines and had probably acquired the infection there. Transmission was probably direct (from patient to patient) or through contact with contaminated surfaces. Treatment with fluoroquinolones during the six months before a culture was obtained was associated with a significant risk of salmonella infection. More fluoroquinolones were used at Nursing Home A than at similar nursing homes in Oregon. The isolates from the outbreak had similar patterns on pulsed-field gel electrophoresis and the same *gyrA* mutations. The isolates from the outbreak were also similar to the only previous isolate of fluoroquinolone-resistant salmonella in the United States, which came from a patient in New York who had been transferred from a hospital in the Philippines.

Conclusions We describe a prolonged nosocomial outbreak of infection with fluoroquinolone-resistant *S. enterica* serotype Schwarzengrund. More such outbreaks are likely in institutional settings, particularly those in which there is heavy use of antimicrobial agents. (N Engl J Med 2001;344:1572-9.)

EACH year an estimated 1.4 million salmonella infections occur in the United States.[1] Most occur as a result of eating contaminated food,[2] particularly foods of animal origin. Person-to-person and nosocomial transmission have become rare in the United States[3] but remain problems in developing countries.[4,5] Antimicrobial agents are not essential for the treatment of most salmonella infections, but they can be lifesaving in cases of severe infection.[6] Fluoroquinolones such as ciprofloxacin are commonly used for adult patients with salmonella infections and for the treatment of acute gastroenteritis. The use of ampicillin, chloramphenicol, and trimethoprim–sulfamethoxazole is limited because of increasing antimicrobial resistance to these agents.[7,8]

Case reports of fluoroquinolone-resistant salmonella infections are rare; only one case has been reported in the United States.[9-12] Most cases have occurred in persons with underlying illness, particularly persons with human immunodeficiency virus infection and with recurrent salmonella septicemia who have been treated with fluoroquinolones. The one previously reported fluoroquinolone-resistant salmonella infection in the United States was detected in 1995, in a patient who had been hospitalized in the Philippines for a diarrheal illness and who was then transferred to a hospital in New York. A stool sample obtained from the patient in New York yielded *Salmonella enterica* serotype Schwarzengrund — a serotype that is rare in the United States — that was resistant to fluoroquinolones.[11]

We report the first recognized outbreak of fluoroquinolone-resistant salmonella infection in the United States, also caused by *S. enterica* serotype Schwarzengrund. This outbreak is notable for two reasons: the salmonella infections were acquired nosocomially, and the outbreak was difficult to control and continued for several years.

METHODS

Outbreak

In February 1997, the Oregon Health Division became aware of an outbreak of *S. enterica* serotype Schwarzengrund infections when three culture-confirmed cases were reported by the health departments of Multnomah and Washington counties. Interviews with the patients revealed that two were current residents and one a past resident of the same nursing home, Nursing Home A (Fig. 1). The index patient had been hospitalized in the Philippines for three months after a severe pontine cerebrovascular accident that occurred during travel and was transferred to a hospital in the United States for long-term care in December 1995. Two months later, a culture of a purulent discharge from the site of insertion of a suprapubic urinary catheter yielded *S. enterica* serotype Schwarzengrund. Stool cultures obtained 12 months later revealed that the patient was still shedding the same organism. The Oregon Health Division inspected Nursing Home A and recommended enhanced infection-control procedures. In March 1997, the Oregon Health Division collected stool cultures from 115 patients and 46 of the 54 staff members in Nursing Home A; none yielded salmonella. Two months later, another case was detected in Nursing Home A. Two cases were also detected in March and September 1997 in a second nursing home, Nursing Home B, located in an adjacent county.

In November 1998, 18 months after the last patient with culture-confirmed salmonella infection was discharged from Nursing Home A, another case was detected there. Isolates were tested for antimicrobial susceptibility and found to be resistant to fluoroquinolones, and the Centers for Disease Control and Prevention (CDC) was invited to join the investigation. In November 1999, another patient with culture-confirmed salmonella infection was identified in Nursing Home A and found to reside in the room that had been occupied by the index patient, who had been discharged 29 months earlier. Thirty samples were collected on swabs from various surfaces and material in the room; two yielded *S. enterica* serotype Schwarzengrund. One of the two samples came from a foam mattress, which was then destroyed. In addition, cultures of

urine and stool from the asymptomatic roommate of the newly infected patient yielded *S. enterica* serotype Schwarzengrund. In March and April of 2000, two more cases were identified. No additional cases occurred during 11 months of follow-up.

Epidemiologic Investigation

Information about the patients was obtained through reviews of medical charts and death certificates and included demographic data, the length of stay, use of antimicrobial agents, gastrointestinal symptoms, results of laboratory cultures, use of invasive procedures, and outcome. To identify possible mechanisms of transmission in Nursing Homes A and B, we interviewed staff members and conducted on-site inspections. To ascertain compliance with infection-control practices, we reviewed the annual surveys and inspection reports for the years 1994 through 1997, which we obtained from the Senior and Disabled Services Division of the Oregon Department of Human Services.

To determine the risk factors for the transmission of fluoroquinolone-resistant salmonella infections in Nursing Home A, the facility with the greater number of patients, we conducted a case–control study. Patients were defined as residents of Nursing Home A from whom fluoroquinolone-resistant *S. enterica* serotype Schwarzengrund was isolated between February 1996 and December 1998. Controls consisted of all 13 residents in the skilled-nursing care area of Nursing Home A who had negative cultures for salmonella in March 1997.

To estimate the quantities of antimicrobial agents used at Nursing Home A as compared with other facilities, we conducted a focused survey of the use of antimicrobial agents in nursing homes in Oregon. We contacted the company that supplies pharmaceutical products to Nursing Home A, the second-largest supplier of pharmaceuticals to nursing homes in Oregon. We requested information on the number of prescriptions for antimicrobial agents that were filled between September 1 and December 16, 1998, at Nursing Home A as well as at three other nursing homes (not including Nursing Home B) of similar size and level of care. These other facilities were selected as a convenience sample by the pharmaceutical distribution company. To standardize the results for
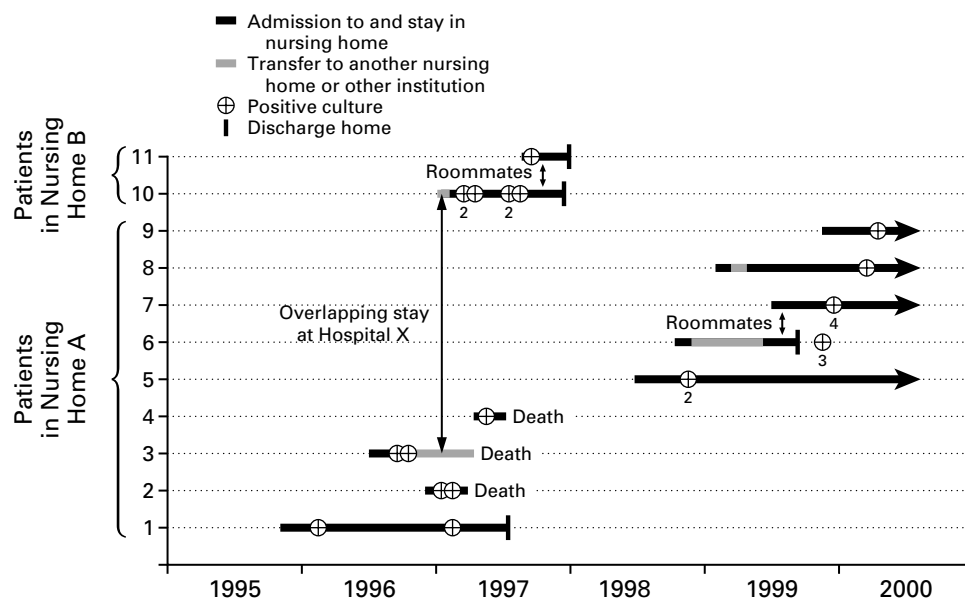
Figure 1. Time Line of Events for 11 Patients with Positive Cultures for *Salmonella enterica* Serotype Schwarzengrund in Oregon, 1995 through 2000.

Patient 6 resided in the room that had been occupied by Patient 1, the index patient. The numbers below the positive-culture symbols for Patients 5, 6, 7, and 10 indicate the number of positive cultures in a given month.

pharmaceutical use in different facilities, we calculated the rate of prescriptions for antimicrobial agents per 100 beds.

Laboratory Investigation

Isolates of *S. enterica* serotype Schwarzengrund were sent to the CDC for antimicrobial-susceptibility testing to determine the minimal inhibitory concentrations (MICs) of a panel of 16 antimicrobial agents by the broth-microdilution method with the use of the semiautomated Sensititre system (Trek Diagnostics, Westlake, Ohio). The guidelines of the National Committee for Clinical Laboratory Standards were used when they were available; an MIC of apramycin of at least 8 μg per milliliter and an MIC of ceftiofur of at least 32 μg per milliliter or more were considered indicative of a resistant organism. Isolates were also tested for resistance to ciprofloxacin with the use of the E test according to the manufacturer's recommendations (AB Biodisk, Solona, Sweden). To determine the mechanism of resistance, we used the polymerase chain reaction (PCR) to amplify the region of the *gyrA* gene in the isolates that determines quinolone resistance and sequenced the region with the use of primers P1 and P2BIO.[13] Primers for PCR and sequencing were synthesized at the Biotechnology Core Facility of the CDC. PCR products were sequenced on an automated sequencer (model 377, Applied Biosystems Division, Perkin–Elmer, Norwalk, Conn.). Isolates were also characterized by pulsed-field gel electrophoresis, as previously described.[14]

Statistical Analysis

We used the Wilcoxon rank-sum test to compare group means for nonparametric data. In the case–control study, we calculated odds ratios and exact 95 percent confidence intervals, and we determined two-tailed P values with use of Fisher's exact test. All statistical analyses were performed with the use of Epi Info software (version 6.04, CDC, Stone Mountain, Ga.).

RESULTS

Epidemiologic Information

A total of 11 persons with culture-confirmed fluoroquinolone-resistant *S. enterica* serotype Schwarzengrund infection (7 women and 4 men) were identified between February 1996 and April 2000. The median age of the patients was 85 years (range, 64 to 90). In nine patients, *S. enterica* serotype Schwarzengrund was first isolated from urine cultures; in one, it was first isolated from a stool culture, and in one from a wound culture. The urine samples had been obtained because the patients had a variety of clinical indications, including cloudy urine, fever, and abdominal pain. In five patients in whom the organism was first isolated from urine or wound culture, subsequent cultures of stool samples yielded *S. enterica* serotype Schwarzengrund. All patients had chronic medical problems. Five had indwelling devices (e.g., a central venous catheter, a urinary catheter, or a nasogastric tube).

Of the 10 patients for whom we had complete information, 9 had been treated with fluoroquinolones in the six months before the collection of the specimen that yielded *S. enterica* serotype Schwarzengrund. The median interval between the use of a fluoroquinolone and a positive culture was 42 days (range, 7 to 124). Two patients were given fluoroquinolones as a treatment for the salmonella infection. Among the nine who were treated with fluoro-

quinolones before the first positive culture, the median duration of treatment was 7 days (range, 5 to 10). Four patients had gastrointestinal symptoms after beginning a course of fluoroquinolone therapy and before having a positive culture. Three patients had diarrhea, two had bloody stools, four had abdominal cramps, three had nausea, two had vomiting, and three had fever.

Nine of the patients with *S. enterica* serotype Schwarzengrund infection were identified in Nursing Home A. An average of 100 patients reside in the facility, where the services provided include rehabilitation, long-term care, and skilled-nursing care. All nine patients resided in the skilled-nursing care area, which has a capacity of 21 beds.

State inspectors identified no deficiencies in the infection-control procedures at Nursing Home A between 1994 and 1997. Two of the 30 environmental samples collected in December 1999 were positive for *S. enterica* serotype Schwarzengrund. These two samples were taken from a foam mattress in the index patient's room and the door handle of that room 29 months after the patient had been discharged. The mattress was stored under the patient's bed, was handled regularly by staff, and was used as a floor bed for the restraining of residents. The mattress was removed and destroyed in December 1999.

During this outbreak, transmission apparently occurred in two hospitals (the hospital in the Philippines and Hospital X) and two nursing homes (Nursing Homes A and B). The index patient most likely acquired the infection during a hospital stay in the Philippines. On his return to Oregon, the patient was brought to Nursing Home A, where he shed the organism for at least 12 months; eight patients were subsequently infected at Nursing Home A. One of these patients was hospitalized at Hospital X on the same day as another patient who had had no contact with Nursing Home A. These two hospitalized patients were given a bath on the same day; however, the records do not indicate where the baths occurred or by whom they were given. The second patient apparently became infected at Hospital X and then went to Nursing Home B, where the infection spread to a roommate.

Five residents of Nursing Home A met the definition of a patient with salmonella infection and were included in the case–control study. They were compared with 13 residents of Nursing Home A who were also cared for by skilled nurses but whose stool samples did not yield *S. enterica* serotype Schwarzengrund in March 1997. The patients with salmonella infections did not differ significantly from the controls with respect to sex, race, age, or presence or absence of an indwelling device (Table 1). The median length of stay in the nursing home was longer for the patients with salmonella infection than for the controls (71 vs. 38 days, P=0.07). The patients with salmo-

TABLE 1. CHARACTERISTICS OF PATIENTS WITH SALMONELLA INFECTION AND CONTROLS IN NURSING HOME A IN OREGON, DECEMBER 1998.

CHARACTERISTIC	PATIENTS (N=5)	CONTROLS (N=13)	ODDS RATIO FOR SALMONELLA INFECTION (95% CI)*	P VALUE
Length of stay — days				0.07
Median	71	38		
Range	37–181	4–4992		
Age — yr				0.59
Mean	80	77		
Range	64–89	53–85		
Female sex — no. (%)	4 (80)	7 (54)	3.43 (0.23–196)	0.60
Non-Hispanic white race — no. (%)	5 (100)	12 (92)	Undefined†	1.00
Indwelling device — no. (%)	3 (60)	5 (38)	2.40 (0.19–33.0)	0.61
Treatment with antimicrobial agent — no. (%)‡				
Fluoroquinolone	4 (80)	2 (15)	22.00 (1.06–1177)	0.02
Trimethoprim–sulfamethoxazole	2 (40)	1 (8)	8.00 (0.28–510)	0.17
Other	3 (60)	5 (38)	2.40 (0.19–36.9)	0.61
Death — no. (%)	3 (60)	5 (38)	2.40 (0.19–36.9)	0.61

*CI denotes confidence interval.

†Because none of the patients were of another racial or ethnic group, an odds ratio could not be computed but approaches infinity.

‡Reported data are for use during the six months before a culture was obtained.

nella infection were more likely than the controls to have taken fluoroquinolones in the six months before a culture was obtained (4 of the 5 patients, as compared with 2 of the 13 controls; odds ratio, 22.0; 95 percent confidence interval, 1.06 to 1177; P=0.02) (Table 1). These four patients took fluoroquinolones a median of 14 days (range, 7 to 55) before their first positive culture. Use of trimethoprim–sulfamethoxazole or other antimicrobial agents in the six months before a culture was obtained was not associated with the acquisition of salmonella infection.

Three of the 5 patients died, as compared with 5 of the 13 controls (P=0.61). In the three patients with salmonella infection who died, the intervals between the last positive culture and death were 3 days, 23 days, and 7 months. The causes of death were pneumonia, intracerebral hemorrhage, and myeloid dysplasia, respectively. Nursing Home A used more fluoroquinolones than the other nursing homes we studied; fluoroquinolones were the most commonly used antimicrobial agents in these facilities (Fig. 2).

Two patients with *S. enterica* serotype Schwarzengrund infection were identified in Nursing Home B. An average of 100 patients reside in this facility, where the services provided include long-term and subacute care. The two patients resided in the subacute care area, and for two months they shared the same room. State inspectors had previously noted deficiencies in infection-control practices at the nursing home. Most recently, the facility had been cited for the failure to add a cleanser during the washing of soiled linens.

Laboratory Results

The isolates from the outbreak were all resistant to ampicillin, ciprofloxacin, and trimethoprim–sulfamethoxazole, and some were resistant to a variety of other agents (Table 2). All isolates from the outbreak had similar patterns on pulsed-field gel electrophoresis, which were also similar to the only previous isolate of fluoroquinolone-resistant salmonella in the United States, a sample of *S. enterica* serotype Schwarzengrund isolated in New York in 1995 (Fig. 3).[11] Four control isolates of *S. enterica* serotype Schwarzengrund collected in Oregon between 1995 and 1998 but not associated with the outbreak had different patterns on pulsed-field gel electrophoresis and were sensitive to ciprofloxacin. The nine ciprofloxacin-resistant isolates we tested had the same two point mutations in the region of *gyrA* that determines quinolone resistance, whereas the control isolates had the wild-type sequence (Table 3). The two point mutations were identical to those seen in the 1995 isolate of ciprofloxacin-resistant *S. enterica* serotype Schwarzengrund from New York.

DISCUSSION

This report describes the first outbreak of fluoroquinolone-resistant salmonella infection in the United States. Between February 1996 and April 2000, 11 patients with laboratory-confirmed infection with fluoroquinolone-resistant *S. enterica* serotype Schwarzengrund were identified in Portland, Oregon. Transmission probably occurred in two nursing homes and
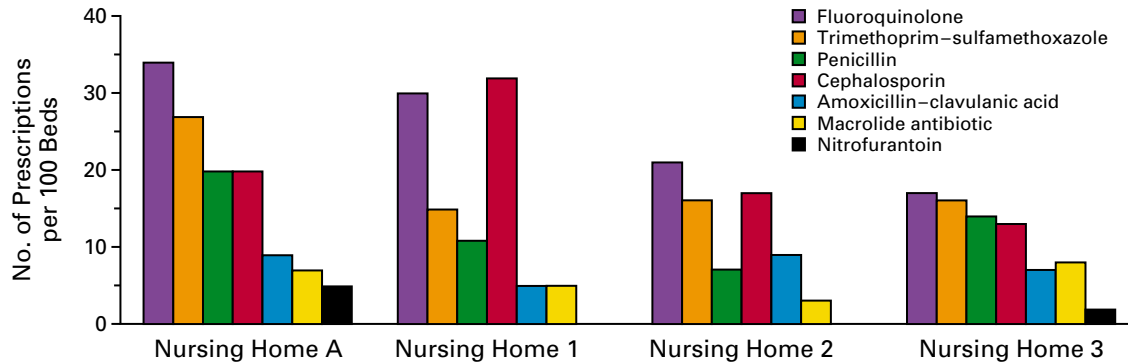
Figure 2. Number of Prescriptions for Antimicrobial Agents in Four Nursing Homes in Oregon, September 1, 1998, to December 16, 1998.

Nursing Home A was the only one of the nursing homes that had patients with culture-confirmed infections with *Salmonella enterica* serotype Schwarzengrund.

TABLE 2. RANGE OF CONCENTRATIONS TESTED, MINIMAL INHIBITORY CONCENTRATIONS OF 16 ANTIMICROBIAL AGENTS, AND NUMBER OF THE ISOLATES OF *SALMONELLA ENTERICA* SEROTYPE SCHWARZENGRUND THAT WERE RESISTANT.

| ANTIMICROBIAL AGENT	RANGE OF CONCENTRATIONS EVALUATED	MIC*	ISOLATES WITH RESISTANCE
	μg/ml		no. (%)
Amikacin	4–32	≤4	0
Amoxicillin–clavulanic acid	0.5–32/0.25–16	8/4	0
Ampicillin	2–64	>32	9 (100)
Apramycin†	2–16	>32	7 (78)
Ceftiofur†	0.5–16	1	0
Ceftriaxone	0.25–16	≤0.25	0
Cephalothin	1–32	8	1 (11)
Chloramphenicol	4–32	>32	5 (56)
Ciprofloxacin‡	0.014–2	>4	9 (100)
Gentamicin	0.25–16	8	3 (33)
Kanamycin	16–64	≤16	0
Nalidixic acid	4–64	>256	9 (100)
Streptomycin	32–356	≤32	0
Sulfamethoxazole	128–512	>512	9 (100)
Tetracycline	4–64	>32	8 (89)
Trimethoprim–sulfamethoxazole	0.12–4/2.4–76	>4/>76	9 (100)

*MIC denotes minimal inhibitory concentration.

†This agent is for veterinary use only.

‡The result of the E test for ciprofloxacin on the isolate from the index patient was 4 μg per milliliter, and the results from all other isolates were more than 32 μg per milliliter.

one hospital in the Portland area. The index patient apparently acquired the infection while hospitalized in the Philippines in 1994 and was subsequently transferred to one of the nursing homes. Of approximately 8000 salmonella isolates tested at the CDC between 1994 and 1998, only 1 other isolate was resistant to fluoroquinolone.[11] That isolate was also *S. enterica* serotype Schwarzengrund and was obtained from a person who had also been hospitalized in the Philippines in 1994.

As in an earlier study that examined previous use of antimicrobial agents as a risk factor for drug-resistant salmonellosis,[15] our case–control study demonstrated that fluoroquinolone use in the six months before the date of specimen collection was significantly associated with an increased likelihood of a fluoroquinolone-resistant salmonella infection. Although trimethoprim–sulfamethoxazole was also widely used in Nursing Home A, its use was not associated with illness in the case–control study. We used a wide window of exposure because we were unable to ascertain precisely the time of onset of illness through review of the medical charts, and the onset was often not associated with specific reported symptoms. The longer exposure period probably increased the extent of nondifferential misclassification (i.e., the incorrect classification of exposure for an equal proportion of patients and controls), making it more difficult to demonstrate an association. Our finding suggests that the use of fluoroquinolones may select for and contribute to the transmission of this fluoroquinolone-resistant strain of *S. enterica* serotype Schwarzengrund, perhaps by lowering the inoculum required to cause infection.[7]

The isolates from the outbreak in Oregon and the isolate from the patient in New York had similar patterns on pulsed-field gel electrophoresis, suggesting
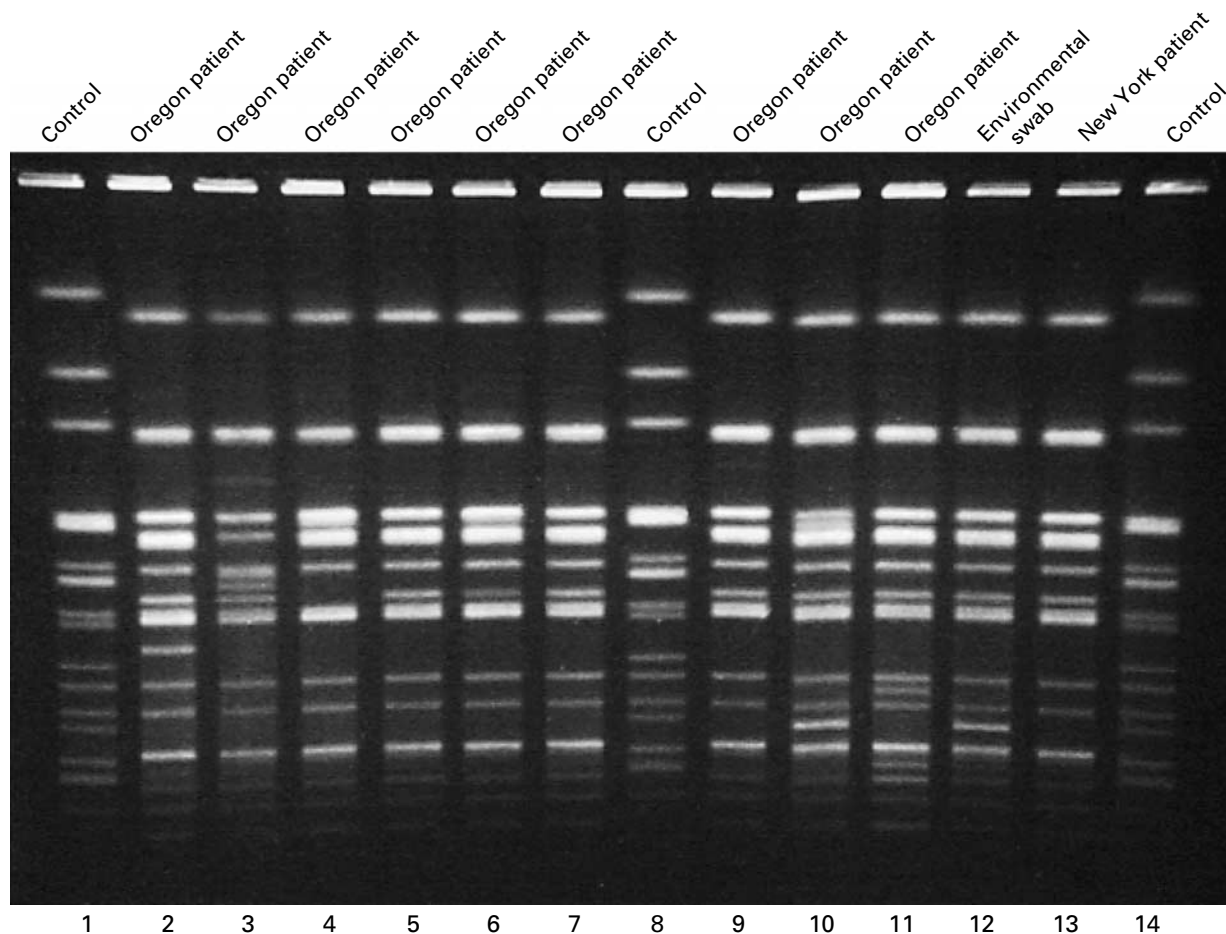
Figure 3. Results of Pulsed-Field Gel Electrophoresis of Fluoroquinolone-Resistant Isolates of *Salmonella enterica* Serotype Schwarzengrund from Oregon and New York.

Lanes 1, 8, and 14 show *S. enterica* serotype Newport controls; lanes 2 through 7 and 9 through 11 show isolates from the nine patients in Oregon; lane 12 shows the environmental isolate from a foam mattress; and lane 13 shows the isolate obtained in 1995 from the patient in New York.

that the infections arose from a common source. The sequencing results support this hypothesis: all isolates had the same two mutations in the *gyrA* gene. Variability in the mutations of the *gyrA* gene has been demonstrated among other fluoroquinolone-resistant isolates.[16,17] Furthermore, these laboratory data are consistent with the epidemiologic data; both the New York patient and the index patient in the Oregon outbreak had been hospitalized in the Philippines. Further investigation revealed that these two patients had been hospitalized in the same facility in Manila, the Philippines. We were also able to ascertain that in 1992 and 1993, the prevalence of fluoroquinolone resistance in nontyphoidal salmonella in the Philippines was 2.5 percent,[18] and by 1998 it had increased to 4.7 percent (Turnidge J: personal communication).

In the Philippines, several factors may contribute to increasing fluoroquinolone resistance, including over-the-counter availability of fluoroquinolones[18] and the use of fluoroquinolones in food animals.[19] The variability in resistance to other antimicrobial agents suggests that different isolates may have acquired different determinants of resistance (e.g., plasmids and integrons).

This investigation documents the transmission of fluoroquinolone-resistant salmonella in the United States. Because fluoroquinolones are the drug of choice for the treatment of severe salmonella infections in adults,[6] the potential continued emergence and dissemination of fluoroquinolone-resistant salmonella are of great concern. In 1999, the Florida Department of Health reported an outbreak of nosoco-

TABLE 3. Sequences of the Fluoroquinolone-Resistance–Determining Regions of the *gyrA* Gene and the Minimal Inhibitory Concentration of Ciprofloxacin in Fluoroquinolone-Susceptible and Fluoroquinolone-Resistant Isolates.

Source of Isolate	Salmonella Serotype	gyrA Codon									MIC of Ciprofloxacin (µg/ml)*
		80 His	81 Gly	82 Asp	83 Ser	84 Ala	85 Val	86 Tyr	87 Asp	88 Thr	
GenBank†	Wild type	CAC	GGC	GAT	TCC	GCA	GTG	TAT	GAC	ACC	—
Oregon but not related to outbreak	Schwarzengrund	—	—	—	—	—	—	—	—	—	≤0.01
Outbreak in Oregon	Schwarzengrund	—	—	—	_T_‡	—	—	—	_G_§	—	≥4
New York	Schwarzengrund	—	—	—	_T_‡	—	—	—	_G_§	—	≥4

*MIC denotes minimal inhibitory concentration. An MIC of 4 µg per milliliter or higher is considered to indicate resistance.

†The GenBank accession number is X78977.

‡The change results in the substitution of phenylalanine for serine at position 83.

§The change results in the substitution of glycine for aspartic acid at position 87.

mially acquired fluoroquinolone-resistant *S. enterica* serotype Senftenberg infections at a medical facility; the similarities between the Florida and Oregon outbreaks are striking.[20] The transmission, perhaps through environmental contamination, apparently occurred within medical facilities — a circumstance that should raise questions about the transmissibility of a highly resistant organism.

The reservoir for most nontyphoidal salmonella in the United States is food-producing animals, and therefore the emerging resistance of salmonella is largely a consequence of the use of antimicrobial agents in animals. This outbreak was unusual because it occurred in medical facilities and involved person-to-person transmission. In the developing world, nosocomial and community-acquired multidrug-resistant salmonellosis has been a recurrent problem.[4,5,21] The origins of resistance in the developing world are unknown.

Since enhanced infection-control practices were implemented in the United States in the 1970s, nosocomial outbreaks of salmonella have been rare. The emergence of highly resistant salmonella in an environment characterized by heavy use of antimicrobial agents may provide a setting that is conducive to nosocomial transmission.[4] The outbreak we studied was difficult to control and lingered for several years. The environmental contamination and the duration of fecal shedding, as well as the characteristics of the facilities,[22] may have contributed to the prolonged nature of the outbreak.

Those involved in infection control in hospitals, as well as public health authorities, should be aware that fluoroquinolone-resistant salmonella has arrived in the United States, and clinicians should consider drug-resistant salmonella in the differential diagnosis of nos-

ocomial infections. Nursing homes should evaluate their infection-control procedures and implement appropriate changes. Additional studies may be needed to determine where antimicrobial agents are being used in a nonjudicious manner. Finally, this outbreak underscores the need for the judicious use of antimicrobial agents in all domestic and international settings.

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